REMARKS/ARGUMENTS

Status of the Claims.

Claims 1, 3-6, 12-15, 17, 19-23, and 25 are currently pending in this application. Claims 1, 6, and 12 are amended herein as per the Examiner's suggestion to make the language and terminology consistent amongst the claims. Support for such language change is replete throughout the specification and claims as filed. For example, support for such changes can be found on, *e.g.*, page 17, lines 6-10 of the specification. The changes are made without prejudice and are not to be construed as abandonment of any previously claimed subject matter or agreement with any objection or rejection of record. Accordingly, entry of the Amendment is respectfully requested.

The present Office Action rejected claims 1 and 12 under 35 U.S.C. §112, first paragraph due to language usage and claims 1, 3-6, and 12 under 35 U.S.C. §112, second paragraph for lack of antecedent basis. Claims 1, 3-6, 12, 13, 17, 19-23, and 25 were rejected as allegedly obvious under 35 U.S.C. §103(a) as to Kramer *et al.* (1995) in view of Urschel *et al.* (1990), Althaus (WO 9303140), Unger *et al.* (EP 731,108) and Unger *et al.* (1995) and in further view of Weiner *et al.* (USPN 5,935,577). Additionally, claims 14 and 15 were rejected under 35 U.S.C. §103(s) as allegedly obvious as to Kramer *et al.* (1995) in view of Urschel *et al.* (1990), Althaus (WO 9303140), Unger *et al.* (EP 731,108) and Unger *et al.* (1995) and in further view of Hammang *et al.* (USPN 5,904,144) and The Merck Manual (p. 1091). Applicants respectfully amend in part and traverse in part.

Amendments to the Claims.

Claims 1, 9, and 12 are amended herein to correct antecedent basis issues and to clarify language. Such changes do not present new matter. Therefore, entry of the amendments is respectfully requested.

35 U.S.C. §112.

Claims 1 and 12 were rejected in the current Office Action as allegedly lacking enablement under 35 U.S.C. §112, first paragraph. Claims 1, 3-6, and 12 were further

rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Applicants herein amend.

Claims 1 and 12 were rejected due to their use of the term "preventing" in their final lines. The Examiner helpfully suggested that Applicants change the term "preventing" to "suppressing." In order to further prosecution, and as per the Examiner's suggestion, Applicants herein amend claims 1 and 12 to change "preventing" to "suppressing." Support for such word change can be found through the application and claims as filed. For example, as pointed out in the Response filed June 16, 2003, support for use of "suppressing" can be drawn from the definition of "suppress" in view of the data presented throughout the specification. For example, page 17, lines 6-10 and page 17, line 14 through page 18, line 4 (along with Tables 2 and 3 and Figure 4) show lessened demyelination in subjects treated with NGF as opposed to those not so treated. *See, e.g.*, Table 3 comparing inflammation/demyelination of neural regions of rhNGF treated subjects and placebo treated subjects. Such data (and similar data throughout the application as filed) shows a suppression of demyelination, since a common meaning of "to suppress" is defined as "to inhibit the growth or development of." *See, e.g.*, Merriam-Webster Online, www.m-w.com, at "suppress."

Claims 1, 3-6, and 12 were rejected due to lack of antecedent basis for the term "prevent." With entry of the above amendment changing "preventing" to "suppressing," the claims no longer contain the term "prevent" or "preventing." Since the claims no longer include "prevent" or "preventing" there can be no lack of antecedent basis for the terms.

Because the wording upon which the 35 U.S.C. §112 rejections were based has been removed, Applicants respectfully request that the rejections be withdrawn.

35 U.S.C. §103(a).

Claims 1, 3-6, 12, 13, 17, 19-23, and 25 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kramer *et al.* (*Nature Medicine*, 1995, 1(11):1162-1166) in view of Urschel *et al.* (*Journal of Comparative Neurology*, 1990, 296:114-122), Althaus (WO 9303140), Unger *et al.* (EP 731,108) and Unger *et al.* (1995, Poster: 25th Annual Meeting Society for Neuroscience, San Diego, CA, USA November 11-16, 1995) and in further view of Weiner *et al.* (USPN 5,935,577). Applicants respectfully traverse.

A *prima facie* case of obviousness from combined references requires that the combination of the cited art, taken with general knowledge in the field, must supply all of the elements of the claimed invention. M.P.E.P. §2143.03. Additionally, there must be a motivation or suggestion to modify the reference(s) or combine the teachings to produce the claimed invention. M.P.E.P. §2143.01 and *In re Geiger*, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Furthermore, there must be a reasonable expectation of success. M.P.E.P. §2143.02 and *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed Cir. 1988). The required teaching or suggestion to combine the references, and the expectation of success, must both be found in the prior art and not based upon the disclosure of the Applicants. M.P.E.P. §2142. Again, Applicants respectfully point out that these requirements have not been met for a *prima facie* showing of obviousness for combinations of the cited references.

The cited references fail to meet *prima facie* obviousness because, *e.g.*, there is no motivation or suggestion to combine them. Thus, even assuming, *arguendo*, that the references supply all the necessary claim elements, *prima facie* obviousness is still not present since there is no motivation/suggestion to combine the references.

The Office Action characterizes the teachings of the cited references (especially those of Unger (EP 731,108)) in a number of ways so that they allegedly would be obvious to combine. However, Applicants respectfully disagree with the Office Action's reading of the references and, thus, the Office Action's assertion of motivation/suggestion to combine and, thus, of obviousness.

The Office Action cites to language in Unger (EP 731,108) which states that "the identification and characterization of factors which are responsible for increased regeneration of OL [oligodendrocytes] is very important for the molecular understanding of demyelinating diseases, such as multiple sclerosis and for the development of therapeutic agents." *See* Unger, col. 1, lines 18-23. From this, the Office Action states that there is "a close relationship between regeneration and degeneration of myelin" and that "demyelination and remyelination are closely related." However, Applicants respectfully submit that such statements from the Office Action are overly broad given the citations from the references. While the text of Unger may imply that increased regeneration of oligodendrocytes would help understand diseases such as MS, it does not state or imply that demyelination and

remyelination are closely related. Understanding of a complex disease such as MS involves multiple facets and areas (*e.g.*, oligodendrocytes and their actions, myelin (as separate from oligodendrocytes), etc.). Thus, a statement that demyelination and remyelination are closely related is an overly broad reading of the cited quote.

The Office Action is somewhat closer to the mark when it states that "the ordinary artisan would have expected that the results in one area concomitantly provide relevant information for a related area of **research**." Office Action at page 5, emphasis added. Thus, in other words, it presents an invitation to experiment, which is not a legitimate basis for establishing obviousness. *See, e.g., Ex Parte Erlich*, 3 USPQ2d 1529 (Fed. Cir. 1988); *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987); *In Re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); and *In Re Eli Lilly & Co.* 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Courts have repeatedly held, motivation/suggestion to combine cannot be established by pointing to passages that invite experimentation to see if something will work.

Therefore, at most, the references present an invitation to experiment, not a motivation/suggestion to combine, and thus, there is no *prima facie* obviousness.

The cited references also fail to present *prima facie* obviousness because there is no reasonable expectation of success, fully achieving the desired invention, in combining the references. As previously stated, even if Kramer, *arguendo*, contains statements concerning decreasing demyelination in rodent neurons, there is no expectation of success in combining it with the rat model in Urschel and the porcine/human in Althaus, etc. Again, as pointed out in the specification at page 19,

> It is important to recognize that, due to the interspecies differences in the biological effects of growth factors and the differential expression of their specific receptors, information derived from rodent studies may not be applicable to humans.

Such passage highlights the lack of expectation of success for combination of such references. The Office Action cites to Weiner *et al.* (USPN 5,935,577) for support that there was an expectation of success in combining the various animal models of the many references cited. However, as is stated in the quotation from the specification above, key differences between models (*e.g.*, between rodent/rat/mouse and human/nonhuman primate, etc.) do exist. Further support for the viewpoint that various animal models are not always

predicative of human equivalence can be found in, *e.g.*, Van Regenmortel, *EMBO Reports*, 2004, 5(11):1016-1020, which questions the "wisdom of extrapolating data that are obtained in mice to other species." Also, the National Heart, Lung, and Blood Institute's Strategic Plain for Fiscal Years 2005-2009 (available online at www.nhlbi.hig.gov/resources/docs/plan/treat.htm) states that "[a]nimal models of human disease are not always sufficient to test the efficacy of experimental therapies." Thus Applicants submit that there was no reasonable expectation of success in combining data from the various animal models in the numerous references cited.

Additionally, other factors also emphasize why no expectation of success exists in combining the references. For example, while again, *arguendo*, Kramer might concern decreased demyelination, Althaus focuses on regeneration of myelin, while, Urschel is even further away in that it focuses on showing that removal of NGF affects myelination (not that adding NGF increases myelin). Thus, the references concern different actions/aspects of myelin (*e.g.*, regeneration of myelin rather than demyelination, decreased demyelination, etc.) and there would be no reasonable expectation of success in combining them.

Applicants note that the references are not being argued against individually by stating their differences. Rather, by stating their differences it is emphasized how they each concentrate on different areas and, thus, there would be no expectation of success, fully achieving the desired invention, in combining the references

Finally, the combinations of the cited references do not even present all the elements of all of the current claims. For example, they do not include NGF (as used in claims 17-25) in an effective amount sufficient to downregulate the production of interferon γ by T cells infiltrating the central nervous system. The Office Action states that "administration of NGF would naturally have this effect on a human or nonhuman primate . . . since it is a property of NGF." Office Action at page 5. However, the Office Action does not give support for such assertion (*e.g.*, citation to a reference or the like).

In sum, the cited references fail to meet the three required aspects of *prima facie* obviousness because there is no motivation/suggestion to combine the references, there is no expectation of success in combining the references, and not all elements of the claimed invention are present in the references. Therefore, Applicants respectfully request that the rejections be withdrawn.

Claims 14 and 15 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kramer *et al.* (*supra*) in view of Urschel *et al.* (*supra*), Althaus (WO 9303140), Unger *et al.* (EP 731,108) and Unger *et al.* (*supra*) and in further view of Hammang et al. (USPN 5,904,144) and The Merck Manual (p. 1091). Applicants respectfully traverse.

As illustrated above, there is no motivation/suggestion to combine, nor expectation of success in combining Kramer, Urshel, Althaus, Unger, and Unger. Because there is no underlying motivation/expectation tying Kramer, Urshel, Althaus, Unger, and Unger together, there is no motivation/expectation of success to add Hammang or Merck. In other words, the combination of references against claims 14 and 15 fails for similar reasons as stated above.

Thus, the cited references fail to meet the required aspects of *prima facie* obviousness because there is no motivation/suggestion to combine the references, and there is no expectation of success in combining the references. Therefore, Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3507 to schedule an interview.

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Respectfully submitted,

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